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Impact of Comorbid Depressive Disorders on Subjective and Physiological Responses to Emotion in Generalized Anxiety Disorder

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Abstract

Generalized anxiety disorder (GAD) and unipolar depressive disorders (UDD) have been shown to differ from each other in dimensions of affective functioning despite their high rates of comorbidity. We showed emotional film clips to a community sample ($n = 170$) with GAD, GAD with secondary UDD, or no diagnosis. Groups had comparable subjective responses to the clips, but the GAD group had significantly lower heart rate variability (HRV) during fear and after sadness, compared to controls. While HRV in the GAD and control groups rose in response to the sadness and happiness clips, it returned to baseline levels afterwards in the GAD group, potentially indicating lesser ability to sustain attention on emotional stimuli. HRV in the GAD + UDD group changed only in response to sadness, but was otherwise unvarying between timepoints. Though preliminary, these findings suggest comorbid UDD as a potential moderator of emotional responding in GAD.

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Compliance with Ethical Standards

Conflict of Interest Saren H. Seeley, Douglas S. Mennin, Amelia Aldao, Katie A. McLaughlin, Jonathan Rottenberg, and David M. Fresco declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Animal Rights No animal studies were carried out by the authors for this article.

Keywords

Generalized anxiety disorder; Heart rate variability; Emotion; Comorbidity

Introduction

Generalized anxiety disorder (GAD) is highly comorbid with unipolar depressive disorders (UDD) including major depressive disorder and dysthymia (Hoffman et al. 2008; Kessler et al. 2005). Efforts to differentiate transdiagnostic from disorder-specific features of GAD and UDD continue to represent a challenge for both research and clinical efforts; perhaps consequently, these disorders tend to be most disabling and refractory to treatment when they co-occur (Barrera and Norton 2009; Garcia et al. 2015; Mennin and Fresco 2013; Zimmerman and Chelminski 2003). Given considerable genotypic and phenotypic overlap in addition to lifetime and concurrent comorbidity, some scholars suggest that GAD and UDD are better subsumed under a broader category of ‘distress disorders’ within a hierarchical structure of arousal and positive and negative affect (e.g., Brown et al. 2001; Gorwood 2004; Watson 2005). A counterpoint to these structural models comes from the difficulty they have in accounting for contextual factors, or functional relationships in affective functioning (e.g., Brown and Barlow 2005; see Mennin et al. 2008). In order to discriminate disorder-specific phenomena from transdiagnostic markers of psychopathology, it will be important to clarify the nature of *response heterogeneity*, or differences in response to emotion, as a function of comorbidity. In this study, we examined physiological response to emotion-eliciting film clips in a large community sample of adults with GAD or GAD with secondary UDD, and non-diagnosed controls.

Emotions provide us with a sense of our goals and needs and facilitate our ability to make decisions and navigate our environment (e.g., Frijda 1986). Yet, intensely-felt emotions can also become highly distressing and disabling (Gratz and Roemer 2004; Gross and Jazaieri 2014). The arousal associated with normal emotional experiences, even positive experiences, can feel unpleasant or even threatening, and thus become translated as anxiety to individuals with GAD (e.g., Llera and Newman 2014; Mennin et al. 2007). Worry functions as an attempt to dampen this arousal, or to attenuate aversive shifts between contrasting emotional states—for example, joy and disappointment (e.g., Borkovec et al. 2004; Llera and Newman 2014). Much distress in UDD as well as in GAD stems from internally-mediated attempts to manage emotions (e.g., Borkovec et al. 2004; Fresco et al. 2002; Kertz et al. 2012; Mennin and Fresco 2013; Nolen-Hoeksema et al. 2008). However, UDD is marked by dampened intensity and reactivity, in contrast to the typically heightened emotionality associated with GAD (e.g., Mennin and Fresco 2015; Rottenberg et al. 2005a).

One mechanism through which heightened intensity might give rise to later blunted emotional responding is the prolonged suppression of autonomic arousal associated with chronic worry (e.g., Borkovec et al. 2004). Autonomic nervous system (ANS) activity is a central part of how we experience emotions (Bradley and Lang 2000; Gross 1998; Kreibig 2010). *Heart rate variability* (subtle beat-to-beat changes in heart rate) results from fluctuating ANS influence on cardiac function (see Shaffer et al. 2014). HRV is thought to

reflect the functional integrity of a central autonomic network that plays an integral role in facilitating communication between brainstem and forebrain structures (e.g., hypothalamus, amygdala, medial prefrontal cortex) and visceral organs, including the heart, in service of self-regulation (see Thayer et al. 2012). Typically, non-anxious individuals demonstrate rapid physiological adaptation to stressors, reacting strongly to threats, but then returning quickly to baseline once the threat is past. However, chronically anxious individuals show weaker responses and delayed recovery (e.g., Hoehn-Saric and McLeod 2000; Lyonfields et al. 1995). HRV is a well-suited measure of this type of flexible (or inflexible) responding, as an index of the ability to dynamically adjust to physical, cognitive and emotional challenges in the environment (e.g., Appelhans and Luecken 2006; Geisler et al. 2010; Porges 2007; Thayer and Lane 2000). Decreased HRV is associated with inhibitory deficits common to GAD such as threat bias, perseveration, and prolonged physiological arousal (Friedman 2007; Thayer and Lane 2009). Lower HRV in GAD may indicate a defensive and disorganized response style in which physiological rigidity mirrors an inflexible cognitive and behavioral repertoire that is typified by worry and avoidance (e.g., Aldao and Mennin 2012; Movius and Allen 2005; Thayer et al. 1996).

Numerous studies support an association between anxiety disorders and decreased HRV (Chalmers et al. 2014). However, not all studies have shown significantly different resting state, or tonic, HRV in individuals with GAD relative to controls (e.g., Aldao and Mennin 2012; see Chalmers et al. 2014). Importantly, the extant literature suggests that there may be moderators of the reduced HRV in GAD. One such factor is likely to be the presence of comorbid UDDs. Decreased parasympathetic activity may underlie the higher rates of cardiovascular disease observed in major depressive disorder (MDD; e.g., Nahshoni et al. 2004; Udupa et al. 2007; van der Kooy et al. 2006). However, lower tonic HRV may not represent a stable and robust marker of depression (c.f. Brunoni et al. 2013); for example, the meta-analysis by Rottenberg (2007) found that MDD diagnosis explained just 2 % of overall variance in tonic HRV. Decreased tonic HRV may also be secondary to anticholinergic properties of some antidepressants (e.g., Kemp et al. 2014a; Licht et al. 2008), or attendant symptoms of depression such as low mood or poor sleep (Bylsma et al. 2014; Salomon et al. 2013). By contrast, there is more consistent support for dysregulated HRV in at the phasic level in MDD, evidenced by decreased physiological reactivity to emotional stimuli (e.g., Rottenberg et al. 2005a; Rottenberg et al. 2007; Salomon et al. 2009; Yaroslavsky et al. 2013). This dampened reactivity reflects a larger pattern of 'emotional context insensitivity' which may represent an endophenotype for depression (Bylsma et al. 2008; Yaroslavsky et al. 2014).

Few studies have explored how HRV responses to emotion in GAD might vary as a function of comorbid depression. Kemp and colleagues (2012) found decreased HRV in patients with MDD, compared to individuals with no psychiatric diagnosis; further, the comorbid MDD + GAD group exhibited the lowest HRV relative to MDD-only and control groups. Likewise, in a sample of Taiwanese patients, individuals with GAD and comorbid MDD showed the lowest levels of HRV relative to individuals with GAD alone, though HRV was reduced in both groups relative to controls (Chang et al. 2013). However, both studies focused solely on tonic HRV. In contrast to the above studies, Hofmann and colleagues (2010) found that GAD individuals without comorbid MDD displayed consistently lower HRV than those with

comorbid depression throughout experimentally-induced worry and relaxation as well as at baseline. Examining HRV on a phasic level (i.e., in the context of emotional responding) may therefore provide additional insight into the role of emotional experience in GAD psychopathology. Indeed, Llera and Newman (2010) found that worry increased general negative affect in individuals with GAD, yet decreased both physiological and/or subjective reactivity to fear and sadness stimuli. Although the greater cognitive load associated with chronic worry alone has been suggested to underlie the relationship between GAD and decreased HRV, other studies have demonstrated reduced HRV in emotional contexts independent of worry (e.g., Pieper et al. 2007; Verkuil et al. 2009), and it will be important to clarify whether dysregulated physiological activity in emotional contexts represents a transdiagnostic or disorder-specific feature of GAD and comorbid depression.

It is also notable that no study to date has yet specifically examined the impact of comorbid UDD (either dysthymia or major depressive disorder) on HRV in GAD. While there have been few HRV studies specifically contrasting dysthymia to MDD, there is some evidence that there may not be meaningful differences between these diagnostic categories. For example, Harte et al. (2013) found no differences in HRV between participants in their sample with dysthymia versus those with MDD, and suggest that the specific diagnosis may not have an effect on HRV above and beyond simply meeting the diagnostic threshold for a depressive disorder. Given that MDD and dysthymia have similar rates of comorbidity with GAD (e.g., Watson 2005), a sample featuring GAD individuals with comorbid UDD, rather than MDD alone, should increase ecological validity of any observed effects.

In the current study, we presented film clips used widely in previous studies of emotion and HRV (e.g., Rottenberg et al. 2007) to a community sample of adults in three groups: a) individuals with GAD alone, b) individuals with primary GAD with secondary UDD (GAD + UDD), and c) healthy controls. We recorded subjective and physiological responses to emotional (fear, sad, happy) film clips, as well as at baseline and during a brief recovery period. We predicted that individuals with GAD and GAD + UDD would show distinct patterns of physiological response to emotion that differed from controls and from each other. We expected that GAD + UDD and non-comorbid GAD groups would exhibit different patterns of HRV responses to the film clips such that individuals with GAD alone would show more phasic activity across the experiment as a function of heightened emotional intensity, whereas those with GAD + UDD would show a less differentiated pattern of HRV response to emotional contexts. This was based on earlier similar investigations (e.g., Aldao et al. 2013; Hofmann et al. 2010; Llera and Newman 2010), as well as evidence from prior studies suggesting that comorbid depression may moderate heightened emotional reactivity in GAD and other anxiety disorders (e.g., Taylor-Clift et al. 2011; Weinberg et al. 2012). Finally, we expected to see that self-reported emotion across the experiment would differ between GAD-only and comorbid GAD + UDD groups in one of two directions: 1) that the GAD + UDD group would demonstrate blunted subjective emotion reactivity (i.e., lower affect ratings) across emotional contexts, or 2) that negative affect ratings would be elevated in the GAD + UDD group as a function of greater severity.

Method

Participants

As part of two larger studies of emotion in affective disorders, individuals with and without GAD and depressive disorders were recruited from the greater New Haven, CT ($n = 138$) and Kent, OH communities ($n = 38$) surrounding Yale and Kent State Universities through flyers placed in local papers, on campus, and online through Craigslist (<http://craigslist.org>). Criteria for inclusion in the present sample were a primary DSM-IV diagnosis (American Psychological Association 2013) of either GAD ($n = 58$) or primary GAD with secondary unipolar depressive disorder (GAD + UDD; MDD $n = 22$, dysthymia $n = 14$). Controls ($n = 76$) met no criteria for any diagnosis. Individuals with a primary diagnosis of any other Axis-I disorder—including psychotic, adjustment, substance, or bipolar disorders—were ineligible to participate. Also ineligible were participants with a systemic medical condition (e.g., heart disease, epilepsy), or who were currently taking medications known to directly affect cardiac function (e.g., beta blockers). The majority of the sample as a whole identified as female (64.8 %) and White (63.6 %), with a mean age of 28.00 ($SD = 8.89$). Sample characteristics in each of the three groups, including secondary diagnoses and other medication use, are described in Table 1. The two sites did not significantly differ in terms of gender, $F(2,155) = .168$, $p = .867$, but Yale participants ($M_{age} = 30.04$, $SD = 8.75$) on the whole were older than Kent State participants ($M_{age} = 19.70$, $SD = 1.84$), $t(149.74) = -12.01$, $p < .001$, given that Yale imposed an additional criterion that excluded current undergraduates.

Procedures

Diagnostic Assessment—Prospective participants were scheduled for a diagnostic interview (Structured Clinical Interview for the DSM-IV—Research Version [SCID-IV-RV]; First et al. 2002) conducted by advanced clinical psychology graduate students who had completed a rigorous six-month training on diagnostic assessment using the SCID-IV-RV. Interviewers had to achieve reliability in their diagnoses with experienced diagnosticians before conducting assessments independently. A proportion of the interviews were video-recorded for training and supervision purposes, and an additional rater (AA) watched a subset (25 %) of these recordings in order to code for each diagnosis of GAD and depressive disorders, κ 's from .89 to 1; for other disorders, κ 's from .70 to .85). One departure from the SCID procedures was that the assessment protocol for the present study disregarded the hierarchy rule (i.e., GAD that only co-occurs with UDD is an epiphenomenon of depression, rather than a separate diagnosis), given evidence to suggest that there are few if any meaningful differences between individuals with a DSM-IV GAD diagnosis and those who would otherwise meet the diagnostic threshold for GAD except for the hierarchy rule (e.g., see Zimmerman and Chelminski 2003).

Experimental Session—Several days after the diagnostic interview, participants returned for the experimental session during which they completed self-report measures and the emotional videos task. After a research assistant set up the psychophysiological equipment, participants sat quietly for a 5-min resting baseline recording. They then viewed the fear, happy and sad film clips in counterbalanced order. After each of the film clips, participants

provided state emotion ratings. A physiological recovery period also followed each film, during which participants remained seated while resting for 2 min. The experimental session also involved completing several other computerized tasks not described here, which were counterbalanced with the film clips task. Procedures for the diagnostic interview and emotional videos task were identical at the two sites. All participants provided informed consent, and were compensated 30 dollars for their time. The study was approved by the Institutional Review Boards of Yale University and Kent State University.

Emotion Elicitation—Participants viewed film clips from the movies *Silence of the Lambs* (fear), *Frequency* (happiness), and *Return to Me* (sadness) that have been widely used for emotion induction in previous investigations of anxiety and depression (e.g., Aldao and Mennin 2012; Llera and Newman 2010; Rottenberg et al. 2007). Stimuli were presented with Superlab 4.0.7 (Superlab, Cedrus, Inc. San Pedro, CA, USA) on a desktop computer.

Psychophysiological Set Up—The electrocardiogram (EKG) was recorded using two disposable pre-gelled 11-mm Ag/AgCl electrodes (EL503; Biopac Systems, Inc., Goleta, California, USA), connected to an ECG100C amplifier for the MP150 System (Biopac Systems, Inc.). Respiration and electrodermal activity (not described here) were recorded simultaneously via their respective transducers. A research assistant helped participants to secure the strain gauge respiration belt around their chest and place the electrodes for the EKG in a modified lead-II configuration on their right shoulder and left hip. The EKG was acquired continuously in AcqKnowledge 3.9 (Biopac Systems, Inc.) and digitized at a sampling rate of 1 kHz with high- and low-pass filters at .5 and 35 Hz.

Heart Rate Variability—EKG data in each segment (baseline, emotion film clips, recovery periods) were exported as a series of interbeat intervals (IBIs) in milliseconds from AcqKnowledge for cleaning and processing using QRSTool and CMetX software (Allen et al. 2007; <http://psychofizz.org>). Both programs have shown good field validity (Hibbert et al. 2012). QRSTool interpolates the IBI series in a graphical user interface for semi-automatic R-peak detection, followed by visual inspection and manual correction of any missed beats. CMetX calculates various time-domain metrics of HRV from the cleaned data, including the mean square difference of successive IBIs (MSD), which has previously shown ability to distinguish GAD from non-GAD participants (e.g., Thayer et al. 1996; Aldao and Mennin 2012; Aldao et al. 2013; Mankus et al. 2013). Data segments containing excessive artifacts due to movement or interference were excluded from analysis (Berntson and Stowell 1998). To further reduce the likelihood of artifact contamination, we standardized the resulting HRV values as Z-scores in SPSS 20.0 (IBM Corp, Armonk, NY) and values more than three standard deviations from the mean were removed, checked against the CMetX output that indicates whether any additional artifacts were identified in the cleaned data. MSD values were positively skewed (skewness statistic [2), so we performed a logarithmic transformation on MSD in each segment, which reduced skewness statistics to 1 or lower. Subsequently, ‘HRV’ refers to the log10-transformed MSD.

Self-Report Measures

Baseline Measures—In line with previous studies (e.g., Hofmann et al. 2010) we administered self-report questionnaires to assess levels of the defining clinical features of our diagnoses (i.e., worry in GAD; depressive symptoms in UDD).

Beck Depression Inventory-II (BDI-II)—The BDI-II (Beck et al. 1996) is a widely-used measure of depressive symptom (e.g., anhedonia, irritability, sleep disturbance, tearfulness, excessive guilt) presence and severity within the previous 2 weeks. BDI scores in the present sample showed high internal consistency (Cronbach's $\alpha = .93$).

Penn State Worry Questionnaire (PSWQ)—The PSWQ (Meyer et al. 1990) assesses the degree to which one's worry is pervasive, uncontrollable, and excessive, and is considered a 'gold standard' measure of GAD-relevant worry. Cronbach's $\alpha = .95$ in the present sample.

Worry and Rumination Visual Analog Scales (WVAS and RVAS)—In order to examine whether any observed differences between comorbid and non-comorbid GAD groups might be a result of differences in worry or rumination at the time of the experiment, we also asked participants to rate their present level of each at baseline. Participants were provided with operational definitions of worry and rumination and asked to construct two visual-analogue scales using idiographic anchors. They provided five scenarios from their own lives associated with different levels of worry or rumination, from zero ('none') to 100 ('extreme'), then used these as a frame of reference to rate their level of worry and rumination at that moment. This type of idiographic VAS has previously been used to measure worry at the state level (e.g., McLaughlin et al. 2007; Aldao et al. 2013).

Subjective Emotion Ratings—At baseline and after each of the four film clips, participants completed a modified Positive and Negative Affect Schedule (PANAS; Watson et al. 1988) that we expanded to include three different words within each target emotion (amusement/happiness/joy; dejection/sadness/unhappiness; anxiety/fear/nervousness.) Each emotion was rated on a nine-point scale from 'none' to 'extreme' and averaged into composite scores for happiness ($\alpha = .89$), sadness ($\alpha = .86$), and fear ($\alpha = .82$), all of which demonstrated excellent internal consistency.

Results

Baseline Measures

There was no effect of group (GAD, GAD + UDD, controls) on HRV at baseline, $F(2,143) = 1.525$, $p = .219$.

As expected, we observed a significant main effect of group (GAD, GAD + UDD, controls) on the BDI, $F(2,136) = 63.74$, $p < .001$ and PSWQ, $F(2,146) = 58.29$. BDI scores in the GAD + UDD group ($M = 23.44$, $SD = 8.31$) were significantly greater than in the GAD group ($M = 15.27$, $SD = 8.51$) or in the control group ($M = 5.77$, $SD = 6.13$), $p < .001$. PSWQ scores did not differ between the GAD group ($M = 62.88$, $SD = 10.75$) and the GAD

+ UDD group ($M = 63.62$, $SD = 9.67$), $p = 1.000$, but were significantly lower in the control group ($M = 40.15$, $SD = 15.14$) than in either GAD or GAD + UDD groups, $p < .001$.

There was also a significant main effect of the three-level group on baseline ratings for the RVAS, $F(2,141) = 10.60$, and WVAS, $F(2,141) = 13.75$, $p < .001$. Ratings did not differ significantly between the GAD group (RVAS: $M = 41.79$, $SD = 29.53$, WVAS $M = 43.93$, $SD = 29.33$) compared to the GAD + UDD group (RVAS: $M = 54.48$, $SD = 36.37$, WVAS $M = 54.00$, $SD = 32.29$), $p = .182$. Both groups' ratings were higher than those in the control group (RVAS: $M = 25.86$, $SD = 25.86$, WVAS: $M = 23.35$, $SD = 25.23$), $p = .003$.

Manipulation Check

We conducted a 2 (baseline versus fear, sad, or happy film clip) $\times$ 3 (group) ANOVA for each of the three composite emotions (fear, sadness, and happiness.) There were significant within-subjects effects of period for fear, $F(1,161) = 79.43$, $\eta_p^2 = .33$, for sadness, $F(1,159) = 180.17$, $\eta_p^2 = .53$, and for happiness, $F(1,159) = 50.28$, $\eta_p^2 = .24$, all $p < .001$, such that ratings for each target emotion were greater during the film clip compared to baseline. Table 2 shows mean ratings and their standard deviations for the three emotions in each period by group.

Subjective Response to Emotion

We next examined effects of group on the target emotion at baseline and during the film clip in order to assess potential differences in subjective emotion ratings between GAD, GAD + UDD, and control groups (Table 2).

Fear—There was a small though significant effect of group, $F(1,161) = 15.12$, $p = .009$, $\eta_p^2 = .06$. Pairwise comparisons showed that baseline fear ratings in the GAD group were higher than those in the control group, $p = .001$, but lower than those in the GAD + UDD group, $p = .031$. However, fear ratings during the fear clip were similar across groups, $p = .52$.

Sadness—There was a significant effect of group on sad ratings during baseline and the sad clip, $F(1,159) = 7.28$, $p = .001$, $\eta_p^2 = .08$, such that sadness ratings both at baseline and during the sad clip were significantly lower in both the GAD group, $p = .048$, and the control group, $p = .013$, compared to the GAD + UDD group. There was no significant difference in sadness between the GAD and control groups, $p = .621$ in either period.

Happiness—There was no between-subjects effect of group on happiness, $F(1,159) = 1.51$, $p = .224$, $\eta_p^2 = .02$, and no differences in happiness between groups either at baseline or during the happy film clip.

Physiological Response to Emotion

To examine differences in phasic HRV response to emotion as a function of GAD or comorbid GAD + UDD, we conducted repeated-measures ANOVAs in each of the emotion elicitations (fear, sadness, or happiness). Descriptive statistics for HRV in each time period by group are shown in Table 3. Each model predicted HRV in the three time periods over the

experiment (baseline, film clip, and recovery) from the three-level group, controlling for age and medication. F statistics are reported with Greenhouse-Geisser correction where there was a significant violation of sphericity assumption (Mauchly's test $p < .05$). Overall, there were significant between-subjects effects of age and use of tricyclic antidepressants, SSRI/SNRIs, and benzodiazepines across the various emotional contexts in all three models (Table 4).

Fear—We found no significant main effect of period, $F(2,250) = .57, p = .57, \eta_p^2 = .005$, nor group, $F(2,125) = 1.57, p = .213, \eta_p^2 = .024$ on HRV. However, there was an interaction between period and group, $F(4,250) = 2.78, \eta_p^2 = .043, p = .027$, such that HRV did not differ between groups with the exception of during the film clip, where the GAD group showed significantly lower HRV ($M = 1.38, SD = .22$) compared to the control group ($M = 1.47, SD = .27$), $p = .024$. There was no change in HRV over time in the GAD group, unlike the control group who showed a significant increase from HRV to the fear video, $p < .001$. There was also a trend for this pattern of lower HRV in the GAD group ($M = 1.38, SD = .22$) relative to the control group ($M = 1.48, SD = .28$) continuing in the recovery period, $p = .086$, where HRV in the control group remained elevated relative to their HRV at baseline, $p < .001$. There were no differences between the GAD + UDD group and either the control or GAD groups. HRV in each group over the three time periods is shown in Fig. 1a.

Sadness—We found no significant main effect of period, $F(1.88,228.21) = 1.12, p = .329, \eta_p^2 = .009$, nor group, $F(2,121) = 1.90, p = .154, \eta_p^2 = .03$ on HRV, though there was a just-significant interaction between period and group, $F(3.77,228.21) = 2.53, \eta_p^2 = .04, p = .045$. HRV did not differ significantly between groups at baseline nor during the film clip. During the recovery period, the GAD group showed lower HRV ($M = 1.35, SD = .25$) compared to the control group ($M = 1.45, SD = .25$), $p = .017$, as well as the GAD + UDD group ($M = 1.44, SD = .24$) though only at the trend level, $p = .071$. Interestingly, HRV in both the GAD and GAD + UDD groups declined significantly (p 's $\leq .049$) from the sad clip to the recovery period, while HRV in the control group showed no such change, remaining elevated relative to baseline, $p < .001$. HRV in each group over the three time periods is shown in Fig. 1b.

Happiness—Again, there were no significant main effects on HRV of either period, $F(1.80,221.44) = 1.10, p = .334, \eta_p^2 = .009$, or group, $F(2,123) = 1.38, p = .324, \eta_p^2 = .018$. However, unlike the negative emotion elicitations, there was no interaction effect, i.e., no differences between groups in any period, $F(3.60,221.44) = 0.71, p = .574, \eta_p^2 = .011$. Despite this finding, we did observe that individuals in the control group showed a significant increase in HRV from baseline to the happy clip, $p < .001$, a difference which was maintained during the recovery period (recovery $>$ baseline $p = .014$). Although the GAD also showed an increase in HRV from baseline to the clip, $p = .024$, their HRV during the recovery period did not differ significantly from either baseline or the happy clip. The GAD + UDD group showed no physiological response to the happy clip, as evidenced by no significant pairwise comparisons for HRV between the three periods, $p \geq .288$. HRV in each group over the three time periods is shown in Fig. 1c.

Discussion

The ability to adapt to our mutable environment is fundamental to health and well-being (e.g., Aldao et al. 2015; Friedman 2007; Gross and Jazaieri 2014; Shaffer et al. 2014). In order to explore potential differences in emotional responding in GAD as a function of UDD comorbidity, we presented film clips designed to elicit fear, sadness, and happiness to a large community sample of individuals with GAD, comorbid GAD + UDD, and or no disorder. In summary, we observed significant interaction period-by-group effects on HRV during our negative emotion elicitations (fear and sadness), though not the happy elicitation. Although there was no difference in HRV between groups at baseline, the GAD group displayed significantly lower HRV during the fear film clip and sadness recovery period compared to the control group, while there was no significant difference between the comorbid GAD + UDD group compared to either the GAD group or controls at any timepoint. There were no group differences for happiness. Further, when we compared differences among timepoints within each group, we noticed a pattern of varying phasic responses. In response to all three emotions, controls' HRV increased from baseline to the emotion film clip. Controls' HRV also remained elevated relative to baseline during the recovery periods for fear and sadness. HRV in the GAD group also increased from baseline to film clip (in response to sadness and happiness only); however, individuals with GAD were unable to sustain these increases in HRV during the recovery period. Finally, the GAD + UDD group showed little phasic response to emotion apart from a transient increase in response to sadness; however, HRV did not differ significantly from either the GAD-only or control groups at any timepoint in the experiment.

These patterns of physiological responding among the three groups are particularly interesting in light of our findings with the subjective emotion ratings. Though we found significant effects of group for fear and sadness ratings, these differences appeared to be driven primarily by group differences at baseline (fear) or baseline and the clip (sadness). For both of these emotions, the comorbid group endorsed higher levels of negative affect relative to both GAD and control groups. At baseline, the GAD group endorsed higher levels of fear (but not sadness) compared to the control group. There were no differences between groups in happiness ratings at baseline or during the happy clip. These results might suggest that pre-existing (i.e., unrelated to the elicitation stimuli) negative affect in individuals in the GAD + UDD group may have had a dampening effect on their capacity for responding physiologically to the film clips, in line with the literature showing that depressed individuals are less sensitive to varying emotional contexts (e.g., Bylsma et al. 2008; Rottenberg et al. 2005b). It is also notable that, for the control group, HRV was augmented during the film clips and sustained in the recovery period. In contrast, individuals with GAD alone showed no phasic change in HRV (fear), or showed a transient increase in HRV, which ultimately fell back to baseline during the recovery period (sadness; happiness). In GAD, physiological inflexibility is thought to reflect a defensive and disorganized response style associated with reliance on avoidance and worry as means to manage intensely-felt emotions (e.g., Aldao and Mennin 2012; Llera and Newman 2010; Movius and Allen 2005; Thayer et al. 1996). Although not pathological in and of itself, greater affective intensity may lead individuals with GAD to adopt a rigid and defensive stance in efforts to cope with emotions

that feel overwhelming or threatening (e.g., Mennin and Fresco 2014). Further, non-diagnosed individuals with high levels of difficulties in regulating emotions show a pattern of HRV response similar to that typically found in GAD: in a recent study, although HRV in both low- and high-difficulties groups decreased in response to negative emotion, the high-difficulties group showed a prolonged decrease that persisted beyond the elicitation into the recovery period (Berna et al. 2014). Decreased HRV has also been linked to facets of emotion regulation deficits relevant to GAD—namely lack of emotional clarity and lower inhibitory control when experiencing negative emotions—even after controlling for anxiety and other covariates, supporting the link between physiological flexibility and adaptive response to emotion (Appelhans and Luecken 2006; Williams et al. 2015).

Greater psychological health is generally associated with a quadratic pattern representing rapid vagal withdrawal and recovery in response to a stressor. Here we observed an opposite response, where the film clips were associated with HRV augmentation rather than withdrawal. Although the patterns of HRV response to emotion observed in our sample may seem paradoxical, HRV was lowest during baseline for all groups. This may have resulted from anticipatory stress as participants sat quietly waiting for the experiment to begin in earnest. People often prefer doing *something*, including self-administering electric shocks, to being alone with their thoughts for as little as 6 min (Wilson et al. 2014). Further, higher HRV has been proposed to index increased self-regulatory effort or the ability to sustain attention and engage with stimuli in the environment (e.g., Porges et al. 1994; Segerstrom and Nes 2007), so we might interpret the prolonged increase in HRV in the control group as indicative of greater ability to self-regulate or to sustain attention compared to the GAD and GAD + UDD groups. Although speculative in absence of state worry measures during the film clips and recovery periods, it may be that the periods in which HRV was lower in the GAD group were those periods which led to greater worry. This could be either due to efforts in the recovery period to avoid emotions aroused by the film clips—or simply due to the anticipatory or ambiguous nature of the portions of the experiment that required participants to simply sit and wait for the next stimulus to occur. The lack of HRV augmentation in response to the film clips (other than sadness) in the GAD + UDD group might reflect blunted reactivity (e.g., Bylsma et al. 2008), deficits in motivated attention that are typically more specific to depression (e.g., Chantiluke et al. 2012), or simply greater severity in the comorbid group. Though GAD and GAD + UDD groups did not differ on our measures of worry symptoms (PSWQ) or state worry and rumination (WVAS/RVAS), the GAD + UDD group reported greater overall subjective negative affect, as well as higher levels of depressive symptoms (BDI) compared to both GAD-only and control groups. However, any conclusions regarding differences between the comorbid and non-comorbid groups should be interpreted with caution, given that we did not find any significant differences when comparing HRV in the GAD + UDD group to the other two groups.

Our results are qualified by a number of limitations, most notably the lack of a fourth, UDD-only group, which would have allowed us to assess whether observed effects were unique to depression in the presence of generalized anxiety, or a feature of UDDs themselves. Studies have shown an inverse association between depression severity and tonic HRV (see Kemp et al. 2010, for a meta-analysis), and HRV has been suggested to be an indicator of treatment response (e.g., Balogh et al. 1993; Chambers and Allen 2002) or as a protective factor

against future depressive episodes under certain conditions (e.g., Hopp et al. 2013). Yet others have failed to find these relationships (e.g., Rottenberg 2007; Royster et al. 2012). Heterogeneous samples and methodology may have been one source of such contradictory findings (Rottenberg 2007; van Zyl et al. 2008). The DSM-5 currently categorizes recurrent MDD and dysthymia under the umbrella of ‘persistent depressive disorder’ in absence of meaningful evidence for their differentiation (American Psychiatric Association 2013). Previous studies have also combined MDD and dysthymia (Aldao et al. 2010; Liverant et al. 2008). However, a notable limitation is that there have been few if any studies directly comparing HRV in MDD and dysthymia. Future investigations should seek to better characterize psychophysiological differences (or lack thereof) between individuals with MDD and dysthymia, given the changes to these diagnoses in the DSM-5. To test whether there were meaningful differences between the two diagnoses, we ran our HRV analyses in only in the subsample of GAD + UDD individuals, using specific UDD (MDD versus dysthymia) as a between-subjects factor. We observed no significant effects of having a comorbid dysthymia versus comorbid MDD diagnosis (p 's = .164–.675), nor any diagnosis $\times$ period interactions (p 's = .266–.648). However, our sample of 22 individuals with MDD and 14 individuals with dysthymia may have been underpowered to detect differences. Indeed, the control group in the present study was substantially larger than either GAD or GAD + UDD groups, itself an additional limitation. The sample used in this study were recruited as part of a larger study examining multiple emotion-related phenomena in mood and anxiety disorders, and the control group was used for multiple purposes within this larger study. In addition, we elected to drop a number of individuals from the diagnosed group who had characteristics that made them unsuitable for the present investigation. These included primary diagnosis of another Axis-I disorder (e.g., social anxiety, panic disorder), current substance abuse or dependence, or a depression diagnosis accompanied by the specifier “in full remission” or “in partial remission” that was reflected in a BDI score in the non-depressed range. These decisions contributed to the size discrepancy between the control group and the diagnosed groups. Related to this, another limitation is that lifetime UDD diagnoses were not assessed; therefore it is possible that individuals in the GAD or control groups may have previously had a depressive episode.

Future investigations should employ sufficiently large samples to explore variation within the UDD diagnosis and whether such variations differentially impact responses to emotion. For example, we know little about how depression-as-acute but time limited condition differs from depression-as-chronic mental illness (Monroe and Harkness 2011). Individuals who experience only a single life-time episode of depression have shown comparable emotional startle blink modulation to never-depressed controls, in contrast to individuals with chronic or recurrent forms of depression (Vaidyanathan et al. 2014). Similarly, melancholic and atypical subtypes of depression have been associated with distinctive patterns of physiological reactivity and dysregulation (e.g., Fotiou et al. 2003; Penninx et al. 2013). Melancholia has been shown to feature an overactive stress response indexed by higher heart rate, lower HRV, and elevated serum cortisol, whereas metabolic and inflammatory dysregulation may be more specific to atypical depression (Kemp et al. 2014b; Penninx et al. 2013).

In order to obtain a more complete understanding of how UDD impacts emotional experience in GAD, it likely will be necessary to measure different aspects of physiological activity in addition to HRV. For example, Fisher et al. (2010) found increased sympathetic activity at baseline moderated self-reported physiological arousal in participants with GAD only, whereas there was no relationship between subjective and physiological arousal in comorbid GAD. Further, greater anhedonia and motivational deficits in depression were found to be associated with reduced effort-related sympathetic activity, but were unrelated to HRV (Silvia et al. 2014). SNS measures may be more relevant to ANS dysregulation in UDD than HRV: in a recent study, sympathetic vasomotor tone was found to more strongly predict depressive symptoms than either HRV or blood pressure alone (Sanchez-Gonzalez et al. 2013). ANS dysregulation in GAD has been widely ascribed to the inhibitory effect of chronic worry on specifically parasympathetic flexibility (e.g., Lyonfields et al. 1995; Thayer et al. 1996). Yet the relationship between the SNS and PNS is not necessarily antagonistic (Cacioppo et al. 2007). Unfortunately, the present study did not include a reliable measure of sympathetic nervous system (SNS) activity. Although the CMetX program (Allen et al. 2007) does generate a sympathetic metric, this more accurately indexes shift in autonomic activity (from PNS-dominant to SNS-dominant) rather than degree, as other HRV metrics do, therefore we elected not to include this metric in our present investigation (Toichi et al. 1997). However, future studies should employ reliable measures of sympathetically-mediated cardiovascular activity such as pre-ejection period (i.e., impedance cardiography).

Future studies should also use emotion elicitation procedures that are sufficiently personally relevant and engaging in order to invoke stronger and more complex motivational states (Aldao 2013; Mennin and Fresco 2015). We observed that in general, the film clips did not elicit ratings commensurate with intense subjective emotions. All three groups showed only minor changes in subjective emotion in response to the film clips (Table 2). This may contribute to the small effect sizes associated with the observed changes in HRV and is congruent with the notion that the film clips generally did not elicit a strong emotional response in either subjective or physiological domains. Passively-viewed stimuli may suffer from a lack of personal or motivational relevance, resulting in a less intense emotional experience (Aldao 2013). It is also possible that the three emotions used here are limited in their relevance to GAD psychopathology, in which internally-generated images and thoughts (i.e., worries) may be more evocative than external stimuli (Mennin and Fresco 2015). Therefore, inducing threat or worry states might have been more effective in producing physiological changes comparable to those found in previous studies. Many of these studies involved worry or relaxation inductions—and worry and relaxation have been shown to increase anxiety in GAD (e.g., Heide and Borkovec 1984; Hofmann et al. 2010).

Despite the limitations described above, and although the effects of the film clips on subjective and physiological responses were small, the present study has several strengths, including a large (relative to many investigations of HRV in affective disorders) clinically diagnosed community sample. Given the centrality of emotion to GAD and UDD psychopathology, it is important to understand how affective processes such as generation and regulation are functionally related, as well as how factors such as comorbidity may moderate these relationships (e.g., Mennin et al. 2008; Mennin and Fresco 2015). The

present findings supplement the growing literature showing that GAD is associated with unique emotional and regulatory deficits that differ from deficits found in comorbid GAD + UDD (or UDD alone). Previous studies found patterns of compensatory neural activity in MDD during emotional conflict adaptation, versus impaired conflict adaptation in GAD, blunted emotion-modulated startle-blink in anxiety with comorbid UDD versus anxiety alone, and increased error-related brain activity in GAD versus GAD with comorbid MDD (e.g., Etkin and Schatzberg 2011; Taylor-Clift et al. 2011; Weinberg et al. 2012). These underscore the need to explore how shared characteristics such as negative affectivity might have different functions depending on clinical presentation. For example, GAD typically onsets earlier than UDD in comorbid presentations, so it may be that over time, heightened emotionality could ultimately give way to depressive symptoms such as anhedonia, flattened affect, and motivational deficits (e.g., Kessler et al. 1996; Mennin et al. 2008).

Although these findings results should be regarded as preliminary pending independent replication with a UDD-only group and a stronger emotion elicitation procedure, the lack of baseline differences in HRV here, in contrast to some previous work (e.g., Chang et al. 2013), supports previous findings that suggest that examining change across various contexts (e.g., Hofmann et al. 2010) should better allow dysregulated processes that may not be evident at the tonic level to emerge. For instance, the GAD + UDD group reported elevated depressive symptoms and negative affect at the time of the experiment, which may suggest that their observed lack of physiological response to the film clips might be more related to broader deficits in emotion-related phenomena (e.g., amotivation, anhedonia, and emotion context insensitivity) which can limit individuals from fully engaging with their environment. Indeed, in a previous investigation, we found that greater dispositional positive affect, greater emotional intensity, and approach motivation distinguished GAD from UDD (Aldao et al. 2010). However, unlike controls, individuals in the GAD group did not sustain the increases in HRV that we observed between baseline, and happiness and sadness clips. This could also indicate efforts to avoid attending to emotional stimuli (though does not fully explain the lack of HRV response to the fear clip.) Although any conclusions based on group differences remain speculative at present, given the lack of significant differences in HRV between the GAD-only and comorbid group at any timepoint (and between the comorbid group and controls); however, we hope that the suggestions raised by these findings will guide subsequent investigations to consider comorbid UDD as a potentially important moderator of emotions at a functional level in GAD, even as these disorders share a number of common features.

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Fig. 1.

a HRV during Baseline, Fear, and Recovery by Group. **b** HRV during Baseline, Sadness, and Recovery by Group. **c** HRV during Baseline, Happiness, and Recovery by Group. *Note* age and medications appear as covariates in the model

Table 1

Sample characteristics by diagnostic group

	Group		
	CTL	GAD	GAD + UDD
Demographics % (<i>n</i>)			
Male	40.5 (30)	30.6 (15)	35.3 (12)
Female	59.5 (44)	69.4 (34)	64.7 (22)
African-American/black	5.3 (4)	5.2 (3)	11.9 (5)
Asian	7.9 (6)	8.6 (5)	16.7 (7)
Caucasian/white	44.7 (34)	46.6 (27)	38.1 (16)
Hispanic	5.3 (4)	–	7.1 (3)
Native American	–	1 (1.7)	–
Other	3.9 (3)	5.2 (3)	–
(missing or not provided)	32.9 (25)	32.8 (19)	26.2 (11)
Age M (SD)	26.56 (9.07)	28.44 (9.04)	30.75 (7.75)
Secondary diagnoses (<i>n</i>)			
Attention-deficit disorder	–	1	–
Eating disorder NOS	–	3	1
Obsessive-compulsive disorder	–	2	2
Panic disorder	–	3	5
Post-traumatic stress disorder	–	–	3
Social anxiety disorder	–	11	11
Specific phobia	–	12	11
Medication use (<i>n</i>)			
SSRI/SNRIs	3	5	4
Benzodiazepines	–	1	1
Tricyclic antidepressants	1 ^a	–	–
Hormonal birth control	14	13	4
Antihistamines and allergy	1	2	–
Other (e.g. thyroid, asthma medication)	5	7	3

Data regarding the racial/ethnic makeup of the Kent sample was not available, so information reported (apart from the ‘missing or not provided’ category) is based on the *n* = 144 subsample from Yale. NOS = Not Otherwise Specified

^a Amitriptyline is also used for non-psychiatric purposes (e.g., insomnia, pain, migraine treatment) and results of our HRV analyses did not differ after excluding this individual

Table 2

Emotion ratings in each period (means and standard deviations)

Period	Group <i>M</i> (<i>SD</i>)		
	Control	GAD	GAD + UDD
Baseline			
Fear	0.69 (0.97)	1.42 (1.17)	1.92 (1.50)
Happy	1.91 (1.53)	1.74 (1.14)	1.53 (1.27)
Sad	0.33 (0.78)	0.42 (0.76)	1.12 (1.71)
Fear clip			
Fear	2.64 (2.08)	2.85 (2.00)	2.97 (2.05)
Happy	1.06 (1.21)	0.92 (1.20)	0.94 (1.25)
Sad	0.46 (0.90)	0.44 (1.02)	1.42 (1.90)
Sad clip			
Fear	1.21 (1.32)	1.53 (2.04)	2.32 (1.81)
Happy	1.53 (1.48)	1.20 (1.39)	0.90 (1.05)
Sad	2.15 (1.60)	2.32 (1.76)	3.06 (1.77)
Happy clip			
Fear	0.76 (1.31)	1.07 (1.55)	1.77 (1.57)
Happy	3.03 (1.71)	2.70 (1.70)	2.41 (1.35)
Sad	0.37 (0.98)	0.70 (1.54)	1.29 (1.46)

Emotions were rated on a 10-point scale, where 0 = “none” and 9 = “extreme”

Table 3

HRV in each time period by group (means and standard deviations)

Period <i>M (SD)</i>	Group		
	Controls	GAD	GAD + UDD
Baseline	1.39 (0.28)	1.35 (0.24)	1.41 (0.22)
Fear clip	1.47 (0.27)	1.38 (0.22)	1.45 (0.20)
Fear recovery	1.46 (0.28)	1.38 (0.22)	1.43 (0.25)
Sad clip	1.48 (0.27)	1.41 (0.23)	1.47 (0.22)
Sad recovery	1.45 (0.25)	1.35 (0.25)	1.44 (0.24)
Happy clip	1.46 (0.29)	1.40 (0.24)	1.43 (0.24)
Happy recovery	1.43 (0.25)	1.39 (0.24)	1.43 (0.21)

Table shows the log-transformed *MSD*

Table 4

Between-subjects effects of age and medication type on HRV

Fear	F(1,125)	p	η_p^2
Age *	5.77	.018	.044
Tricyclic antidepressants **	9.06	.003	.068
SSRI/SNRIs *	3.98	.048	.031
Benzodiazepines *	7.98	.006	.060
Hormonal birth control	1.07	.302	.009
Antihistamines/allergy	0.09	.770	.001
Other (misc.)	0.39	.536	.003
Sadness	F(1,123)	p	η_p^2
Age *	4.88	.029	.039
Tricyclic antidepressants *	5.65	.019	.045
SSRI/SNRIs *	6.09	.015	.048
Benzodiazepines *	6.79	.010	.053
Hormonal birth control	1.28	.261	.010
Antihistamines/allergy	0.93	.337	.008
Other (misc.)	0.78	.378	.006
Happiness	F(1,121)	p	η_p^2
Age **	11.18	.001	.083
Tricyclic antidepressants *	6.78	.010	.052
SSRI/SNRIs *	6.38	.013	.049
Benzodiazepines *	5.78	.018	.045
Hormonal birth control	0.61	.437	.005
Antihistamines/allergy	1.15	.285	.009
Other (misc.)	0.27	.603	.002

'Other (misc.)' category includes other medications such as thyroid or asthma medications

*
p < .05;

**
p < .005